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Case report

Fatal bilateral pneumothoraces following administration of aerosolised pentamidine

Alison Green LLB MBBS, Anatomical Pathology Registrar [a],
Nathan Milne MBBS FRCPA MACLM, Forensic Pathologist [a,b,c,*],
Beng Beng Ong MBBS FRCPA FFFLM, Forensic Pathologist [a]

[a] Queensland Health Forensic and Scientific Services, QLD 4108, Australia
[b] The University of Queensland, School of Medicine, QLD 4006, Australia
[c] Bond University, Faculty of Health Sciences and Medicine, QLD 4229, Australia

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ABSTRACT

Aerosolised pentamidine (AP) is used for prophylaxis against infection with *Pneumocystis jiroveci* (*carinii*), a significant cause of morbidity and mortality for people with human immunodeficiency virus (HIV). In this article we report a 55 year old man with HIV and a background history of asthma since childhood, who suffered respiratory arrest and died within an hour of commencing AP prophylaxis. Autopsy revealed bilateral pneumothoraces. Common side effects of AP therapy include bronchospasm and coughing. Pneumothorax has been reported in several cases. To our knowledge, this is the first reported fatality from bilateral pneumothoraces.

1. Introduction

A 55 year old man with known human immunodeficiency virus (HIV) infection attended a HIV clinic for first time administration of aerosolised pentamidine (AP). Prior to the AP therapy, nebulised salbutamol was given to counter the common AP side effect of bronchospasm and cough. The patient reported that he felt well. AP therapy was initiated via nebuliser, and he was then left alone in the pentamidine administration room. A nurse checked on the patient several minutes later, and readjusted the nebuliser flow rate from 2 L/min to 6 L/min, and having once again confirmed the patient was comfortable, left the room. Less than 2 min later the patient approached staff complaining of shortness of breath. He was diaphoretic, dyspnoeic and unable to speak in sentences. He became increasingly unwell and suffered a cardiorespiratory arrest. Cardiopulmonary resuscitation (CPR) and manual ventilation was commenced by clinic medical staff. Ambulance officers arrived 10 min later and they continued CPR and performed an uncomplicated intubation. Resuscitation efforts were attempted for another 20 min without success.

2. Case report

Background medical history included asthma diagnosed at age 13, with several hospital admissions as a child and adolescent, and one four day admission to an intensive care unit at age 40. Prescribed asthma medications at the time of death were budesonide and salbutamol. Occupational history included a single episode of exposure to asbestos. He smoked three to five marijuana cigarettes a week. Recent lung function test results reflected his chronic asthma, with mild reduction in gas transfer.

The patient had been diagnosed with HIV eleven years previously, and had been largely asymptomatic. One month before he died, he was re-started on a highly active antiretroviral therapy (HAART) regimen, after a monitored treatment break due to lactic acidosis as a side effect of his previous regimen. At the time of re-starting HAART, it was considered he had symptoms of disease progression, notably oral thrush, weight loss (5.5% of body weight over the preceding five months) and folliculitis. He was assessed as

* Corresponding author. Forensic Pathology, Queensland Health Forensic and Scientific Services, 39 Kessels Road, Coopers Plains, QLD 4108, Australia. Tel.: +617 3000 9650, +614 3246 2397 (mobile); fax: +617 3274 9201.
E-mail address: nathan_milne@health.qld.gov.au (N. Milne).

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at risk of *Pneumocystis jiroveci* (*carinii*) pneumonia (PCP) and he was considered for prophylactic treatment with trimethoprim with sulfamethoxazole. As he was planning to travel overseas in the short term, it was decided that AP would be administered several days prior to departure to avoid sensitivity to trimethoprim with sulfamethoxazole while overseas.

The death was reported to the Coroner, as required for health care related deaths under the Queensland Coroners Act. The Coroner ordered a full internal autopsy which was performed approximately 24 h after death.

As there is a known association between AP therapy and pneumothorax, post mortem chest radiographs were performed. These showed a large right pneumothorax and a moderately sized left pneumothorax. Neither were tension pneumothoraces.

At autopsy there was no subcutaneous emphysema. Pneumothoraces were demonstrated in both chest cavities, by puncturing them under water. There were non-displaced anterior fractures of left ribs four and five, and right ribs three and five. The parietal pleura adjacent to these fractures was intact. The lungs showed black pigment on the pleural surfaces, especially the upper lobes, and there were also bullae involving all lobes. None of the bullae appeared to be ruptured on examination of the non-inflated lungs. The lungs were not contused. There was no evidence of infection or obvious mucus plugging. There were no other significant macroscopic findings.

Histologic examination of lung tissue demonstrated characteristics of chronic asthma including luminal mucus, basement membrane thickening, smooth muscle hypertrophy and hyperplasia, and an increase in peribronchial inflammatory cells. The latter consists primarily of lymphocytes, but eosinophils are also present. There was also a moderate degree of emphysema, which was considered to be the cause of the bullae, and a mild degree of oedema. There was no evidence of asbestosis or infection, in particular PCP. Histology of the liver showed no features of α1-antitrypsin deficiency. Histologic examination of other major organs revealed no significant pathology and no HIV-related disease.

Microbiological examination of lung tissue was negative for pathogenic bacteria, mycobacteria, fungi, *P. jiroveci*, *Toxoplasma gondii*, cytomegalovirus and Epstein–Barr virus. Blood serology confirmed HIV1 infection, and was negative for hepatitis B and C viruses.

The cause of death was bilateral pneumothoraces secondary to prophylactic AP treatment given in the context of HIV infection. Given the size of the pneumothoraces, and minimal resuscitation injuries, the pneumothoraces were not considered to be secondary to CPR. In this context, acute severe bronchospasm related to AP therapy was not the cause of death. Both asthma and emphysema were considered to be significant conditions contributing to death in these circumstances.

3. Discussion

P. jiroveci (*carinii*) is a common life-threatening opportunistic infection in people with HIV. Pentamidine is a guanidine analogue with antiprotozoal activity. It is used in its aerosolised form for both primary and secondary PCP prophylaxis. It is regarded as a well tolerated agent among the regimens available for prophylaxis.[1–12] AP is delivered, in appropriately sized particles, to the alveoli by a nebuliser.[1]

A 1996 meta-analysis of 35 randomised trials, with more than 6000 patients, compared efficacy and toxicity of prophylaxis regimens including AP and found that there were no deaths attributable to prophylaxis.[3] The meta-analysis revealed thirteen cases of pneumothorax. Reference to the individual studies showed that in one of these cases the patient had suffered from recurrent PCP and in another case *P. jiroveci* had been detected in the patient's sputum.[13] One large study of 408 patients, within the meta-analysis, recorded eight spontaneous pneumothoraces (with six additional pneumothoraces associated with acute PCP, three with bacterial pneumonia and four due to invasive procedures).[12] Discontinuation of AP prophylaxis due to side effects or toxicity was also found within the meta-analysis to be very rare.[3] In cases where AP was discontinued, the reasons for this action included pneumothorax,[12] bronchospasm and cough despite bronchodilator pre-medication,[14,15] bronchoconstriction (without reference to use of bronchodilators),[8] dizziness (in one case 17 months after commencing AP)[12,15] and nausea.[8,12,13]

Recognised common acute side effects of AP include cough and bronchospasm.[1,6,9–13,16–23] Bronchospasm, which can be objectively measured as a decrease in the forced expiratory volume in 1 s (FEV1), is considered to be generally reversible.[1,16–18,20–22] The hypotheses for this side effect include direct irritation to the airways[17] and pentamidine-induced histamine release from mast cells.[21,24] Airway reactivity is increased in patients with HIV who have previously been infected with PCP,[21,24] against a background of generalised airway hyper-reactivity in patients with HIV.[24] The possibility has been suggested that patients who have previously had a PCP infection suffer from progressive sensitisation to AP, which may be mast cell and histamine mediated.[21] AP-related bronchospasm is more likely to occur in patients with hyper-reactive airways, but the magnitude of reduction of FEV1 is not predictable, even where the degree of background airway hyper-reactivity is quantified.[11]

It has been reported that the HIV positive population experiences a higher incidence of adverse reactions to medication in comparison with the general population.[25] Other common adverse effects of AP include gastrointestinal disturbance,[13,16] taste disturbance,[13,16,22] and eye discomfort.[16] Less frequently associated adverse effects include (in addition to widespread pulmonary effects[16] or pneumothorax[1,25,26]), rash,[5,7,16,21,22] raised pancreatic enzymes,[5,16,23] liver function test abnormalities,[16,27] anaemia, neutropaenia and thrombocytopaenia,[6,27] and glucose abnormalities.[16,23] A trial assessing effects of AP on infants and children also noted sneezing and headache.[28]

The incidence rate of pneumothorax amongst patients who have received AP has been quoted as 4% per year and considered similar to the rate amongst historical controls.[23]

Although the mechanism is not fully understood, risk factors for spontaneous pneumothorax in patients with HIV appear to include AP therapy,[29–31] smoking,[29,30,32] cysts seen on chest imaging,[29,30] and past or current infection with PCP.[33–36] The interaction of these risk factors is not clear.

Outside the setting of both HIV and even chronic obstructive pulmonary disease, smoking represents a risk factor for pneumothorax.[30,32] Cysts have been found on chest imaging of patients with HIV who are asymptomatic and have not received AP.[30,37]

A study of eight cases of non-traumatic spontaneous pneumothorax in patients with HIV concluded that the risk factor (for pneumothorax) of past or current infection with PCP appears to be independent of whether or not the patient was treated with AP.[33] A broader study of radiographic PCP trends considered 2424 cases including 1783 patients with HIV and concluded, although the presentation of PCP is highly variable, those patients receiving AP prophylaxis had an increased incidence of spontaneous pneumothorax, cysts and upper lobe disease in contrast to patients who were not receiving AP.[38]

One study's discussion of AP toxicity noted that the statistically significant increase noted in residual volume 'may account for the pneumothoraces seen in patients receiving inhaled pentamidine who could have regions of the lung that are particularly

hyperdistended'.[39] However, another study considering long-term primary AP prophylaxis noted that pneumothoraces, cysts and cavitations had occurred in both the patient group receiving prophylaxis and the group receiving no prophylaxis.[37] A case report of a patient who suffered bilateral pneumothoraces on a background of PCP infection concluded that the infection may cause parenchymal destruction and formation of cysts, and that exudate in small bronchioles may have a ball-valve effect which results in pneumothorax.[29] Another possible contributing factor (not present in this case) is that past or chronic infection with PCP results in fibrotic and/or emphysematous changes in the lung parenchyma (such as bullae[40]), increasing pulmonary vulnerability to pneumothorax.[30,34,41]

Following pneumothoraces in four of 13 patients with haemophilia and HIV, who had received AP primary (1 patient) or secondary (3 patients) prophylaxis between two weeks and 14 months earlier, two hypotheses were put forward: that the pneumothoraces were a late adverse effect of AP or that they were a marker of end stage disease with a background of cystic damage from prior PCP infection.[35]

A case report of two patients with bilateral pneumothoraces found that both had cystic damage in the apices and a history of recurrent PCP. The report surmised that the lung distribution of AP predisposed the patients to apical PCP infection which resulted in cystic damage, the progression of which was most likely to have caused the pneumothoraces. Neither patient suffered pneumothoraces during the delivery of AP.[42] In another report of pneumothoraces in six HIV positive patients with PCP, one had bilateral pneumothoraces.[36]

Although the patient in this case had no evidence of PCP infection, it is possible that existing asthma- and emphysema-related damage played an equivalent role to infection in decreasing pulmonary reserve and increasing the risk of pneumothorax.

Spontaneous pneumothorax is harder to manage in patients with HIV than in patients who are not HIV positive[30] and the prognosis is poor.[34]

4. Conclusion

To our knowledge, this is the first reported fatality from bilateral pneumothoraces due to AP. The patient in this case had a number of risk factors which may have contributed to this fatal adverse reaction to AP. He was a chronic asthmatic, with severe enough disease to have required previous admission to an intensive care unit. He was a smoker. His lungs showed chronic changes of asthma as well as emphysematous changes. His lung function may have been further impaired by generalised HIV-associated airway hyper-reactivity.

Severe adverse reaction to AP is rare and not easily predictable. It would seem that this man's decreased pulmonary reserve was tragically overwhelmed by AP-associated bilateral pneumothoraces.

In the event of a patient dying in the setting of AP therapy, the forensic pathologist needs to be aware of the association with pneumothorax, so that the appropriate examination, including radiology, can be conducted.

This case highlights the importance of a detailed review of the clinical notes prior to performing an autopsy in a health care related death. This is in regard to the circumstances surrounding the death and the deceased's past medical history.

Conflict of interest

None.

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Ethical approval

Ethical approval was not required, however permission was granted by the Coroner for details of the case to be published.

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